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A New Synthesis of Isocoumarins via π-Olefin-Palladium Complex

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Abstraet

The reaction of sodium salts of 2-alkenylbenzoic acids with lithium tetrachloropalladate (II) afforded isocoumarin derivatives. This cyclization reaction is though to proceed by a palladium-assisted nucleophilic attack on the olefin of the alkenyl groups.

Introduction

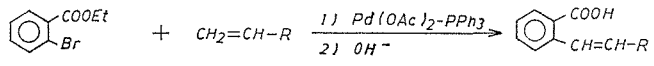
Isocoumarins[1] are a class of naturally occuring lactones which display a wide range of biological activity.[2] It is well known that most of isocoumarin derivatives can be synthesized by cyclizaition of homophthalic acid derivatives,[3] 2-alkenylbenzoic acid derivatives,[4] 2-carboxybenzyl ketones,[5] by the ortho-lithiation of N-methylbenzamides,[6] and by the oxidation of isochromans.[7] These methods frequently suffer from requiring difficult to prepare starting materials and/or severe conditions for cyclization. On the other hand, organometallic reagents have recently been used in the synthesis of a variety of heterocyclic ring system. In particular, an intramolecular nucleophilic attack on palladium complexed olefins has accounted for several heterocyclic syntheses. Thus, α,-β-unsaturated ketoximes were converted to isoxazoles,[8] 2'-hydroxychalcones to flavones,[9] 2'-aminochalcones to 2-aryl-4-hydroxyquinolines,[10] penta-2,4-dienoic acids to 2-pyrones,[11] penta-2,4-dienamides to 2-pyridones,[12] **o**-allylphenols to benzofurans,[13] unsaturated ketoximes to pyridines,[14] α,β-unsaturated alcohol to 2-vinyl-tetrahydrofurans,[15] α,β-unsaturated acyloylureas to 2,6-dihydroxypyrimidines,[16] α,β-unsaturated carbohydrazides to 3-pyrazoles,[17] and α,β-unsaturated hydroxamic acids to 3-isoxazolones.[18] Furthermore, Hegedus **et al** have developed methods, using π-allylnickel halide complex for the facile palladium-assisted cyclization of 2-allylbenzoic acids to isocoumarins[19] and of 2-allylanilines

to 2-alkylindoles.[20] In this report, we wish to describe the newly developed methods to the synthesis of isocoumarins (**1**) from 2-alkenylbenzoic acids (**2**) using palladium (II) salts as a catalyst.

Results and Discussion

Preparation of 2-Alkenylbenzoic Acids (**2**).

Literature methods for the synthesis of **2** are characterized by low yields and intolerance toward functional groups. The well-known palladium-induced vinylic substitution reaction with aromatic halide to introduce an alkenyl group[21-25] offered a more general approach to a variety of **2** (eq. 1).



3　　4　　2

2_a : R=-COOH　　2_e, 4_e : R=-COPh
4_a : R=-COOEt　　2_f, 4_f : R=-Ph
2_b, 4_b : R=-CN　　2_g, 4_g : R=-o-Tolyl
2_c, 4_c : R=-$CONH_2$　　2_h, 4_h : R=-m-Tolyl
2_d, 4_d : R=-$COCH_3$　　2_i, 4_i : R=-p-Tolyl

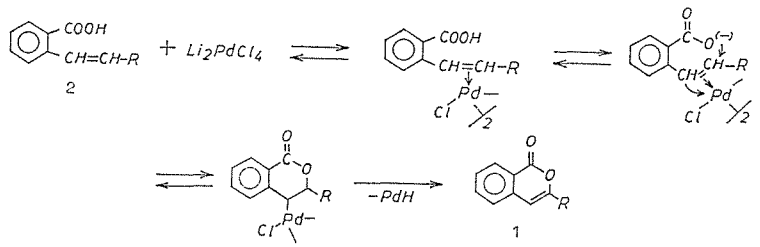
(Eq 1)

Heck *et al* previously reported that *o*-bromobenzoic acid failed to react with methyl acrylate using palladium (II) acetate and tri-*o*-tolylphosphine as catalyst, however, the methyl ester of *o*-bromobenzoic acid did react normally and produce methyl o-methoxycarbonylcinnamate. Thus, treatment of ethyl 2-bromobenzoate (3) with simple olefin (**4**), such as styrene, acrylonitrile, and acrylamide and the subsequent hydrolysis of the reaction product provides a mild and specific synthetic approach to **2**. The reaction carried out and the results obtained are summarized in Table 1.

Cyclization Studies.

Treatment of **2** with lithium chloropalladate (II) and Na_2CO_3 in water led to production of **1** in moderate yield. These results are summarized in Table 2. The reaction is thought to proceed as in eq 2, involving coordination of the olefin to Pd (II), generation of free carboxylate by sodium carbonate, attack of carboxylate on this Pd(II) complex olefin to produce the ring closure and a σ-alkyl-palladium complex, followed by elimination of PdH to the observed isocoumarin. This mechanism is similar to that proposed for formation of indole from 2-allylanilins[20],

and 2'-hydroxychalcone to flavones.[9] The stereochemistry of the ring closure and the state of co-ordination of the carboxylate group prior to attack are not known. Amines[26] and methoxide[27] have been shown to add to Pd (II) complexed olefins in a *trans* fashion, without prior coordination, while hydride[28] adds cis and is coordinated prior attack. Chloride is known to attack by either mechanism, depending on concentration.[29] With all substrates, six-membered ring products are the sole cyclized products. It thus appears that the degree of substitution of the carbon atom to which palladium is bonded prior to β-elimination is of little consequence in determining the ring size of the product.



1_a, 2_a : R=-COOH
1_b, 2_b : R=--CN
1_c, 2_c : R=-$CONH_2$
1_d, 2_d : R=-$COCH_3$
1_e, 2_e : R=-COPh
1_f, 2_f : R=-Ph
1_g, 2_g : R=-o-Tolyl
1_h, 2_h : R=-m-Tolyl
1_i, 2_i : R=-p-Tolyl

(Eq 2)

Experimental

Materials and Anatysis. All the melting points are uncorrected. The IR spectra were measured on KBr disks, using Hitachi 215 spectrometer. The NMR spectra were taken in $CDCl_3$ with TMS as the standard and were recorded with Hitachi R-22 spectrometer at 90 MHz. The mass spectra were obtained with Hitachi RMU-6M mass spectrometer, using a direct inlet and an ionization energy of 70 eV.

General Procedure for the Reaction of Ethyl 2-Bromobenzoate (3) *with Olefin Compounds* (4). A mixture of 10 g (44 mmol) of **3**, 55 mmol of **4**, 0.45g (1.76 mmol) of triphenylphosphine, 0.098 g (0.44 mmol) of palladium(II) acetate, and 5.43 g (55 mmol) of triethylamine in acetonitrile (80 ml) was heated under nitrogen in a sealed tube at 100−110°C for 12 h. The cooled reaction mixture was separated, washed with water, dried over $MgSO_4$, filtered, and concentrated. The residue was then reacted with 20% NaOH aqueous solution at room temperature or at 90-100°C for 12 h. After the reaction mixture was diluted with water and was acidified with 10% HCl aqueous solution. The precipitates was filtered and

purified by recrystallization from ethanol or benzene. The structure of the products was confirmed by a mixed-melting-point determination with an authentic sample and by the observation of the IR and NMR spectra. The results are summarized in Table 1.

Table 1. The Palladium-catalyzed Reaction of Ethyl 2-Bromobenzoate (**3**) with Olefins (**4**).

Olefin	Reaction product (yield)	Mp (℃)	IR and NMR Spectra
CH_2=CH-COOEt (**4a**)	2-(2-Carboxyvinyl)-benzoic acid (**2a**) (42%)	201-203 (lit[a] 203)	
CH_2=CH-CN (**4b**)	2-(2-Cyanovinyl)-benzoic aacid (**2b**) (47%)	177-178 (lit[b] 179)	
CH_2=CH-$CONH_2$ (**4c**)	2-(2-Carbamoylvinyl)-benzoic acid (**2c**) (36%)	192-194	IR: 3100-2500, 1710 (-COOH), 1650 (-$CONH_2$), 1619, 975 cm^{-1} (trans -CH=CH-). NMR: δ 4.22 (br-S, 2H, -$CONH_2$), 6.78 (d, 1H, -C=CH-CO, J=16 Hz), 7.16-7.88 ppm (m, 6H, Ar-H + -COOH + -CH=C-CO). MS: m/e 191 (M^+). Found: C, 62.70; H, 4.58; N, 7.18%. Calcd for $C_{15}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33%.
CH_2=CH-$COCH_3$ (**4d**)	2-(2-Acetylvinyl)-benzoic acid (**2d**) (58%)	115-116	IR: 3100-2500, 1710 (-COOH), 1680 (C=O), 1630, 960 (trans -CH=CH-). NMR: δ 2.14 (s, 3H, -CH_3), 7.16 (d 1H, -C= CH-CO, J=16 Hz), 7.48-7.95 (m, 5H, Ar-H + -COOH), 8.44 ppm (d, 1H, --CH=C-CO, J=16 Hz). MS: m/e 190 (M^+). Found: C, 69.31; H, 5.11%. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30%.
CH_2=CH-COPh (**4e**)	2-(2-Benzoylvinyl)-benzoic acid (**2e**) (70%)	143−145	IR: 3100-2500, 1760 (-COOH), 1680 (C=O), 1610, 960 cm^{-1} (trans -CH=CH-). NMR: δ 6.13 (d, 1H, -C=CH-CO, J=16 Hz), 7.42-8.10 ppm (m, 11H, Ar-H + CH=C-CO + -COOH). MS: m/e 252 (M^+). Found: C, 76.32;

			H, 4.95%. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80%.
CH_2=CH-Ph (**4f**)	2-Styrylbenzoic acid (**2f**) (65%)	158-160 (lit[c] 158-160)	
CH_2=CH-*o*-tolyl (**4g**)	2-(2-*o*-Tolylvinyl)-benzoic acid (**2g**) (54%)	168-169 (lit[a] 169)	
CH_2=CH-*m*-tolyl (**4h**)	2-(2-*m*-Tolylvinyl)-benzoic acid (**2h**) (50%)	156-157 (lit[e] 158)	
CH_2=CH-*p*-tolyl (**4i**)	2-(2-*p*-Tolylvinyl)-benzoic acid (**2i**) (68%)	148-150	IR: 3100-2500. 1740 (-COOH), 1620, 960 cm^{-1} (trans-CH=CH-). NMR: δ 2.31 (S, 3H, $-CH_3$), 6.65 (d, 1H, C=CH-Ph, J=16 Hz), 7.10- 7.65 ppm (m, 10H, Ar-H + -CH=C-Ph + ·COOH). MS: m/e 266 (M^+). Found: C, 80.38; H, 5.77%. Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92%

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General Procedure for the Preparation of Isocoumarins (**1**) *from 2-Alkenylbenzoic Acids* (**2**). A solution of 10 mmol of **2** and 5 mmol of sodium carbonate in water (50 ml) was stirred with 10 mmol of lithium chloropalladate (II) at room temperature. After stirring for 24 h, the reaction mixture was then extracted with ether. The ether extract was washed with aqueous sodium hydrogencarbonate and dried over $MgSO_4$. After the evaporation of the solvent, the product was isolated by recrystallization from ethanol or by column chromatography on silica gel. The structures of the products were confirmed by a mixed-melting point determination and by the observation of the IR and NMR spectra. The results are summarized in Table 2.

Table 2. The Palladium-catalyzed Ring Closure of 2-Alkenylbenzoic Acids (**2**) to Isocoumarins (**1**).

2-Alkenyl-benzoic acid	Product (yield %)	Mp (°C)	IR and NMR Spectra
2a	3-Carboxy-isocoumarin (**1a**) (37%)	232-234 (lit[a] 235)	

2b	3-Cyano-isocoumarin (**1b**) (38%)	117-119	IR: 2250 (-CN), 1760 cm^{-1} (α, β-unsaturated δ-lactone). NMR: δ 7.60-8.06 ppm (m, 5H, Ar-H + -CH=C-). MS: m/e 171 (M^+). Found: C, 69.95; H, 2.89; N, 8.04%. Calcd for $C_{10}H_5NO_2$: C, 70.17; H, 2.94; N, 8.18%
2c	3-Carbamoyl-isocoumarin (**1c**) (36%)	183-184	IR: 1760 (α,β-unsaturated δ-lactone), 1660 cm^{-1} (-$CONH_2$). NMR: (in DMSO-d_6) δ 4.16 (br-s, 2H, -$CONH_2$), 7.68-8.28 ppm (m, 5H, Ar-H + -CH=C-). MS: m/e 189 (M^+). Found: C, 63.38; H, 3.67; N, 7.25%. Calcd for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.41%.
2d	8-Acetyl-isocoumarin (**1d**) (56%)	123-125	IR: 1780 (α,β-unsaturated δ-lactone), 1690 cm^{-1} (C=O). NMR: δ 1.98 (s, 3H, -CH_3), 7.33-8.00 ppm (m, 5H, Ar-H + -CH=C-). MS: m/e 188 (M^+). Found: C, 70.06; H, 4.06%. Calcd for $C_{11}H_8O_3$: C, 70.21; H, 4.29%.
2e	3-Benzoyl-isocoumarin (**1e**) (68%)	125-126	IR: 1760 (α,β-unsaturated δ-lactone), 1690 cm^{-1} (C=O). NMR: δ 7.33-8.11 (m, 9H, Ar-H), 8.40 ppm (s, 1H, -CH=C-). MS: m/e 250 (M^+). Found: C, 76.78; H, 3.86%. Calcd for $C_{16}H_{10}O_3$: C, 76.79; H, 4.03%.
2f	3-Phenyl-isocoumarin (**1f**) (70%)	91-92 (lit[b] 90)	
2g	3-*o*-Tolyl-isocoumarin (**1g**) (65%)	101-102 (lit[c] 102.5)	
2h	3-*m*-Tolyl-isocoumarin (**1h**) (70%)	92-93 (lit[b] 92-93)	
2i	3-*p*-Tolyl-isocoumarin (**1i**) (75%)	114-115 (lit[e] 116)	

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π－オレフィン―パラジウム錯体をへるイソクマリンの新合成法

泉　多恵子・斎藤　修・笠原　晃

工学部　応用化学科

2－アルケニル安息香酸のナトリウム塩と塩化パラジウム酸パラジウムとの反応は，イソクマリン誘導体の生成に導いた。この分子内閉環反応はアルケニル基のオレフィンに対するパラジウム触媒による親核的な攻撃により反応は進むと考えられる。